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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 205/04, A61K 31/395

A1

(11) International Publication Number: **WO 99/37612**

(43) International Publication Date: 29 July 1999 (29.07.99)

(21) International Application Number: PCT/GB99/00219

(22) International Filing Date: 22 January 1999 (22.01.99)

(30) Priority Data:

9801500.1	23 January 1998 (23.01.98)	GB
9824457.7	6 November 1998 (06.11.98)	GB

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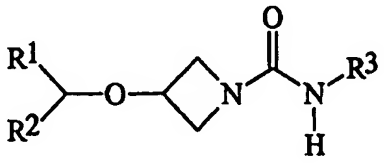
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS



(1)

(57) Abstract

A compound of formula (1), wherein: R^1 is aryl; R^2 is H, alkyl or aryl; and R^3 is hydrogen or alkyl; pharmaceutically acceptable addition compounds thereof; and the use of the compounds in therapy, particularly for the treatment and prophylaxis of CNS disorders such as anxiety and epilepsy.

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AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS

The present invention relates to chemical compounds useful in the treatment of disorders of the central nervous system (CNS), such as anxiety and all forms of epilepsy, particularly in humans. The invention also relates to the use of such compounds, pharmaceutical preparations containing such compounds and to methods of preparing such compounds.

Anxiety disorders affect an estimated 73 million people world-wide. The benzodiazepines have provided the dominant therapy for anxiety over the past three decades and there is no doubt that they are remarkably effective anxiolytics. However, chronic administration of benzodiazepines produces severe dependence liability, withdrawal syndromes, and side effects (sedation, amnesia, muscle relaxation). The only non-benzodiazepine anxiolytic that has been launched over the past decade is the 5-HT receptor ligand buspirone (Buspar®). This drug has had a remarkable commercial success despite being regarded as a weak anxiolytic (compared with the benzodiazepines) and having a long latency to onset of therapeutic action (2-4 weeks). In addition, buspirone and all related 5-HT_{1A} partial agonists suffer from a dose-limiting side-effect profile comprising nausea, vertigo and endocrine changes.

The aetiology of anxiety disorders is not fully understood, but it is now established that benzodiazepines act by potentiating GABAergic neurotransmission although there is strong evidence that other neurotransmitter systems are modulated indirectly - in particular, the serotonergic and noradrenergic systems. Many pharmaceutical companies have invested considerable resource into the development of serotonergic anxiolytics. However, it is now apparent that ligands selective for 5-HT receptor subtypes, despite displaying anxiolytic-like activity in a restricted range of anxiety models, have, at best, very weak and/or non-dose-related anxiolytic effects in the clinic. The 5-HT_3 receptor antagonists are now discredited as psychotropics: they have a restricted range of activity in functional and anxiety models; they show no convincing anxiolytic effects in the clinic; and they are now accepted only as useful anti-emetics. The 5-HT_{2A} antagonists similarly are regarded as ineffective in terms of psychotropic activity. The clinical utility of 5-HT_{1A} receptor agonists and partial agonists is severely limited by their intrinsically weak action and by the dose-limiting side-effects (vertigo, endocrine changes, nausea) which become more intense as the agonist efficacy of these molecules is increased. The selective CCK_B receptor antagonists have displayed an

unimpressive preclinical profile similar to that of selective 5-HT ligands such as the 5-HT_3 antagonists.

Serotonergic anxiolytics include the selective serotonin reuptake inhibitors (SSRIs) which, in addition to displaying antidepressant properties, are also effective in anxiety disorders such as panic disorder and obsessive-compulsive disorder. However, as with their antidepressant action, the major drawback with these compounds is the long delay (6-8 weeks) in the onset of clinical improvement following chronic administration.

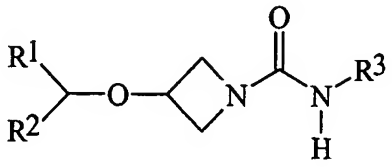
A strategy in recent years towards improving the clinical profile of classical benzodiazepines is that of developing benzodiazepine receptor partial agonists, according to the rationale that they would have a more selective anxiolytic action and be less liable to induce dependence. However, this approach appears to have failed owing to the very weak anxiolytic actions of these compounds and their poor side-effect profiles (there is either a low or non-existent ratio between anxiolytic and sedative doses).

US-4956359 and EP-A-0194112 disclose 3-aryloxy and 3-arylthio azetidinecarboxamides and their anti-convulsant and anti-epileptic activity. These compounds, like the benzodiazepines, have low water solubility which leads to difficulties in formulation. The presence of an oxygen or sulphur atom, present as a linking atom between the aryl group and the azetidine ring, is a key feature of these compounds since such atoms can affect molecular conformation as well as increasing electron density in the aryl rings.

There remains therefore a need for novel anxiolytic and anti-epileptic agents which do not suffer the above-mentioned drawbacks.

It has now been surprisingly found that inserting a methylene-containing group between the aryl group and the oxygen atom, and thereby increasing conformational freedom and decreasing election density in the aryl ring, is not detrimental to pharmacological effect. Further, insertion of the methylene-containing group gives a surprising improvement in the binding affinity to the $GABA_A$ receptor.

According to the present invention there is provided a chemical compound of formula (1)



(1)

wherein:

R^1 is aryl;

R^2 is H, alkyl or aryl; and

R^3 is hydrogen or alkyl;

and pharmaceutically acceptable addition compounds thereof.

Reference in the present specification to an "alkyl" group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic or acyclic the alkyl group is preferably C_1 to C_{12}, more preferably C_1 to C_8 (such as methyl, ethyl, propyl, isopropyl butyl, isobutyl, tert-butyl, amyl, isoamyl, hexyl, heptyl, octyl).

Reference in the present specification to an "aryl" group means a mono or bicyclic aromatic group, such as phenyl or naphthyl.

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 or 2 substituents. Substituents may include:

carbon containing groups such as

alkyl

aryl, arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen containing groups such as

haloalkyl (e.g. trifluoromethyl);

oxygen containing groups such as

alcohols (e.g. hydroxy, hydroxyalkyl, (aryl)(hydroxy)alkyl),

ethers (e.g. alkoxy, alkoxyalkyl, aryloxyalkyl),

aldehydes (e.g. carboxaldehyde),

ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl),

acids (e.g. carboxy, carboxyalkyl),

acid derivatives such as esters (e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkycarbonylyoxy, alkycarbonylyoxyalkyl) and amides (e.g. aminocarbonyl, mono- or dialkylaminocarbonyl, aminocarbonylalkyl, mono- or dialkylaminocarbonylalkyl, arylaminocarbonyl);

nitrogen containing groups such as

amines (e.g. amino, mono- or dialkylamino, aminoalkyl, mono- or dialkylaminoalkyl),

azides,

nitriles (e.g. cyano, cyanoalkyl),

nitro;

sulphur containing groups such as

thiols, thioethers, sulphoxides and sulphones (e.g. alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl);

and heterocyclic groups containing one or more, preferably one, heteroatom, (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl,

pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl).

Preferred substituents include alkyl, aryl, nitrile, halo, or a halogen-containing group such as trifluoromethyl.

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO-.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine or chlorine radical.

The compounds of formula (1) may exist in a number of diastereomeric and/or enantiomeric forms. Reference in the present specification to "a compound of formula (1)" is a reference to all stereoisomeric forms of the compound and includes a reference to the unseparated stereoisomers in a mixture, racemic or non-racemic, and to each stereoisomer in its pure form.

In the compounds of formula (1), preferably R^1 is a substituted or unsubstituted aryl group selected from phenyl and naphthyl, more preferably R^1 is a substituted phenyl or naphthyl, more preferably R^1 is a phenyl or naphthyl having 1 to 3 substituents and most preferably R^1 is a phenyl or naphthyl having 1 or 2 substituents. In a preferred embodiment of the invention, R^1 is a mono- or di-substituted phenyl group, preferably a mono-substituted phenyl group.

Where R^1 is a naphthyl group, R^1 is preferably a 2-naphthyl group.

Where R^1 is a phenyl having 1 substituent, the phenyl group is preferably para- or meta-substituted. Where R^1 is a phenyl having 2 substituents, the phenyl group is preferably 2,4-disubstituted, 2,5-disubstituted, 3,4-disubstituted or 3,5 disubstituted, and more preferably 3,4-disubstituted.

The preferred substituent groups are selected from halo (preferably fluoro and chloro), trifluoromethyl, tertiary-butyl, phenyl and CN.

Where R^1 is disubstituted, it is preferred that R^1 is substituted by two halo groups, the same or different, preferably the same, or by two trifluoromethyl groups.

The most preferred R^1 groups are selected from 3-chlorophenyl, 3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl and 3, 4-difluorophenyl.

In the compound of formula (1), preferably R^2 is H, C_{1-4} alkyl or mono-substituted phenyl. Where R^2 is C_{1-4} alkyl, it is preferred that R^2 is acyclic hydrocarbyl, preferably methyl or ethyl. Where R^2 is mono-substituted phenyl, it is preferred that R^2 is a halo-substituted phenyl, preferably substituted in the para-position.

In one embodiment of the present invention, R^3 is alkyl, preferably C_{1-4} alkyl, and more preferably alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl or unsubstituted saturated cyclic or acyclic hydrocarbyl.

In a further embodiment of the present invention, R^3 is selected from H and C_{1-4} alkyl, preferably from H, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl and unsubstituted saturated cyclic and acyclic hydrocarbyl, and more preferably from H, propyl, 2-propenyl, 2-propynyl and 2-hydroxypropyl.

Particularly preferred compounds are as follows:

R^1	R^2	R^3
4-Cl-C_6H_4	H	2-propenyl
3,4-Cl_2-C_6H_3	H	2-propenyl
3,4-F_2-C_6H_3	H	2-propenyl
3-CF_3-C_6H_4	H	2-propenyl
4-CF_3-C_6H_4	H	2-propenyl
4-F-C_6H_4	H	2-propenyl
4-F-C_6H_4	H	2-propynyl
4-Cl-C_6H_4	H	2-propynyl
4-Cl-C_6H_4	4-Cl-C_6H_4	2-propenyl
4-Cl-C_6H_4	4-Cl-C_6H_4	2-hydroxypropyl
3-CF_3-C_6H_4	H	H
3-CF_3-C_6H_4	methyl	H

Of these, the preferred compounds are 3-(3,4-Dichlorobenzyloxy)-N-(2-propenyl)azetidine-1-carboxamide, 3-(3-(Trifluoromethyl)benzyloxy)-N-(2-propenyl)azetidine-1-carboxamide, 3-(4-(Trifluoromethyl)benzyloxy)-N-(2-propenyl)azetidine-1-carboxamide, 3-(4-Fluorobenzyloxy)-N-(2-propenyl)azetidine-1-carboxamide, 3-(Bis(4-chlorophenyl)methoxy)-N-(2-propenyl)azetidine-1-carboxamide, (R)-3-(Bis(4-chlorophenyl)methoxy)-N-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(1-(3-Trifluoromethylphenyl) ethyloxy)-azetidine-1-carboxamide, and 3-(3-(Trifluoromethyl)benzyloxy)-azetidine-1-carboxamide.

According to a further aspect of the present invention there is provided a compound according to the present invention for use in therapy.

The compounds of the present invention may be used in the treatment (including prophylaxis) of CNS disorders. In particular, the compounds of the present invention may be used in the treatment (including prophylaxis) of anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness, alcohol withdrawal syndrome, chronic and acute pain, neurodegenerative diseases (for example, senile dementia) and

symptoms related to withdrawal from substance abuse. The compounds may also be used in the relief of spasticity. The compounds of the present invention may also be used in muscle relaxation prior to surgery or surgical manipulation or as pre-medication prior to surgery. In a preferred embodiment of the present invention, the compounds are used in the treatment (including prophylaxis) of anxiety or epilepsy.

Anxiety includes generalised anxiety disorder (GAD), panic disorder, panic disorder plus agoraphobia, simple (specific) phobias (e.g. arachnophobia, performance anxiety such as public speaking), social phobias, post-traumatic stress disorder, anxiety associated with depression, and obsessive compulsive disorder (OCD).

Epilepsy is a chronic disorder characterised by recurrent seizures. Two forms of epilepsy exist - partial and generalised epilepsy - and each type is subdivided into idiopathic (cause unknown) or symptomatic (cause known). There are two fundamental types of seizures: partial seizures which includes simple partial seizures, complex partial seizures, and partial seizures secondarily generalised; and generalised seizures which includes generalised tonic-clonic seizures (grand mal), absence seizures (petit mal), myoclonic seizures, atonic seizures, clonic seizures, and tonic seizures.

According to a further aspect of the present invention there is provided use of a compound of the present invention in the manufacture of a medicament for the treatment (including prophylaxis) of CNS disorders, preferably anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness, alcohol withdrawal syndrome, chronic and acute pain, neurodegenerative diseases, symptoms relating to withdrawal from substance abuse or spasticity, and more preferably anxiety or epilepsy.

According to a further aspect of the present invention there is provided use of a compound of the present invention in the manufacture of a medicament for muscle relaxation prior to surgery or surgical manipulation or as pre-medication prior to surgery.

The invention further provides a method of treatment (including prophylaxis) of CNS disorders, preferably anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness, alcohol withdrawal syndrome, chronic and acute pain,

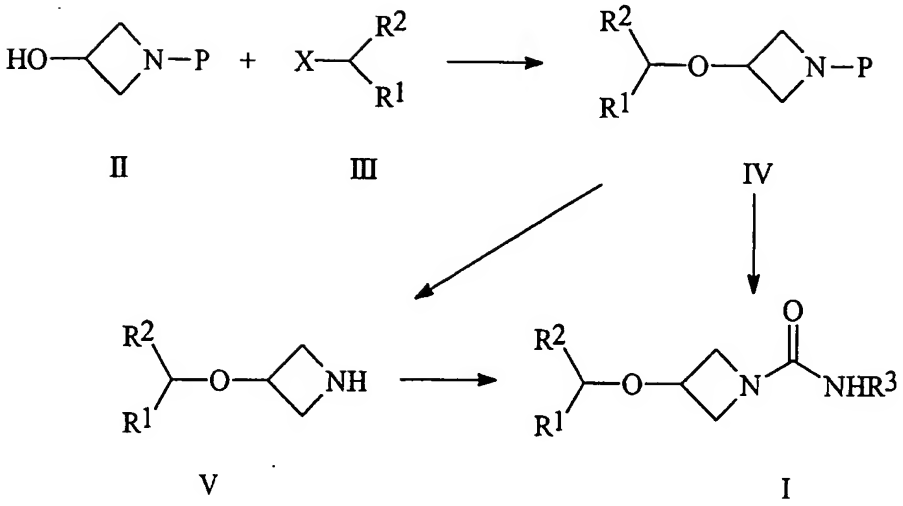
neurodegenerative diseases, symptoms relating to withdrawal from substance abuse and spasticity, and more preferably anxiety or epilepsy, comprising administering to a patient in need of such treatment an effective dose of a compound according to the present invention.

The invention further provides a method of muscle relaxation prior to surgery or surgical manipulation or a method of pre-medication prior to surgery, comprising administering to a patient in need thereof an effective dose of a compound according to the present invention.

According to a further aspect of the present invention there is provided a method of preparing a compound of the present invention.

Compounds of the present invention may be prepared according to the reaction scheme (where P is a nitrogen protecting group). R^1, R^2, and R^3 are as previously defined. The ether (IV) may be formed by reaction of the azetidinol (II) either with an arylalkanol (III, X = OH) and diethylazo dicarboxylate and triphenyl phosphine or with an arylalkyl chloride, bromide, iodide, mesylate or tosylate (III, X = Cl,Br,I, mesylate, tosylate) and a strong base such as sodium hydride. Formation of the azetidine (V) may be achieved by reaction of (IV) with a suitable nitrogen deprotection agent. For example, if P is a diphenylmethyl group, then deprotection may be carried out by treatment with 1-chloroethyl chloroformate followed by methanol. The urea (I) is formed by reaction of azetidine (V) with an N-alkylisocyanate or an N-alkylcarbamoyl chloride and a base such as triethylamine or potassium carbonate. Alternatively, the urea may be prepared directly from the azetidine (IV) without isolation of an intermediate such as the secondary amine (V). For example, when P is a diphenylmethyl group, azetidine (IV) may be treated with phosgene followed by amine R^3NH_2 to give urea (I) directly.

Reaction Scheme



The invention further provides a pharmaceutical composition comprising a compound according to the present invention in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound according to the present invention with a pharmaceutically acceptable carrier or excipient.

Compounds of the present invention may be administered in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use including transmucosal and transdermal use, for example a cream, ointment, gel, aqueous or oil solution or suspension, salve, patch or plaster; for nasal use, for a example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example a finely divided powder or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oil solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients, using standard techniques well known to those skilled in the art of pharmacy. Preferably, the compound is administered orally.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

It will be appreciated that the dosage levels used may vary over quite a wide range depending upon the compound used, the severity of the symptoms exhibited by the patient and the patient's body weight.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

EXPERIMENTAL

Measurement of binding affinity to the $GABA_A$ receptor with $[^{35}S]$- TBPS

The ability of test compounds to bind to the $GABA_A$ receptor was measured in membranes prepared from rat fore-brain using the procedure described by Green *et al* (Green, A.R., Misra, A., Murray, T.K., Snape, M.F. & Cross, A.J. Neuropharmacology, 1996, 35, 1243-1250).

Binding assays were performed in plastic microtitre plates. In each study total assay volume contained $[^{35}S]$-TBPS (1 nM final concentration), membrane preparation and displacing drugs where appropriate. Drug solutions were prepared at a concentration of 10 mM in an appropriate solvent (EtOH, DMSO or H_2O) and then diluted with assay buffer. Non-specific binding was determined using GABA. The free ligand concentration was determined by counting aliquots of the $[^{35}S]$-TBPS solution. The concentration of test compounds required to displace 50% of the specific binding (IC_{50}) was determined from displacement curves. The test results are shown in Table 1

Table 1. Binding Affinities to the $GABA_A$ receptor.

Example number	$IC_{50}(\mu M)$
2	56
3	87
4	91
6	64
7	32

Antagonism of 3-MPA-Induced Seizures

Several animal seizure models are available for the screening and characterisation of anticonvulsant (antiepileptic) drugs. Most models employ a chemical convulsant to induce seizures and the anticonvulsant potencies of novel compounds are measured in terms of their ability to increase the dose of convulsant required to induce a seizure response (or to prolong the latency to seizure onset following a bolus dose of the convulsant). Most chemical convulsants work by blocking the neurotransmitter function of gamma-aminobutyric acid (GABA), the predominant inhibitory neurotransmitter in the mammalian brain. This can be achieved by blocking the postsynaptic action of GABA using pentylenetetrazol or bicuculline, or via a presynaptic action using a GABA synthesis inhibitor to decrease GABA release into the synapse. In this case, the inhibitor of glutamate decarboxylase (GAD), 3-mercaptopropionic acid (3-MPA), was used as the convulsant challenge agent. Anticonvulsant effects of test compounds were determined by their abilities to significantly increase the dose of 3-MPA required to initiate a seizure response.

Male albino T/O strain mice (obtained from Tuck) weighing 28-40 g were used in these studies. Animals were assigned randomly to treatment groups and vehicle or test drug (at a dose of 30mg/kg) were administered p.o. to groups of 12 animals 60 min before the administration of a bolus dose of 3-MPA intravenously. Immediately following 3-MPA administration, each mouse was placed individually into a cage for observation. The seizure response of each animal was scored quantally as present or absent (response or non-response) during the 5 min period immediately following 3-MPA administration. A seizure response was defined as the onset of the initial clonic phase of the seizure (abrupt loss of righting reflex accompanied by vocalisation). The seizure threshold (in terms of mg/kg i.v. of 3-MPA required to evoke a seizure response) was determined in each treatment group by a sequential up/down method followed by modified probit analysis of the quantal data. A range of doses of 3-MPA was prepared (12.5 - 200.0 mg/kg i.v.) increasing by a constant geometric factor ($\sqrt[3]{2}$), which was found in pilot studies to generate suitable data for analysis by this method.

In these studies, 3-MPA was obtained from Sigma.

Test compounds were prepared as solutions dissolved in 45% w/v aqueous 2-hydroxypropyl-ß-cyclodextrin. 3-MPA was dissolved in isotonic saline and its pH adjusted to 6 using 1M

sodium hydroxide solution. Drugs were administered in a dose volume of 10 ml/kg body weight. The test results are shown in Table 2.

Table 2. Antagonism of 3-MPA-Induced Seizures: Results of Testing

Compound	SC	SV
Example 1	35.98	15.7
Example 2	66.7	16.2
Example 3	129.3	15.6
Example 4	75.7	16.2
Example 5	42.8	15.6

SC = seizure threshold after treatment with test drug

SV = seizure threshold in vehicle treated group

Measurement of anxiolytic activity in mice using the elevated zero-maze model.

The elevated "zero-maze" is a modification of the elevated plus-maze model of anxiety which incorporates both traditional and novel ethological measures in the analysis of drug effects (Shepherd, J.K., Grewal, S.S., Fletcher, A., Bill, D.J. and Dourish, C.T., Behavioural and pharmacological characterisation of the elevated "zero-maze" as an animal model of anxiety. *Psychopharmacology,* **1994**, *116*, 56-64).

Male Sprague-Dawley rats (Charles River) weighing 300-450 gm are used. Animals are group-housed (5 per cage; cage size: 40 x 40 x 20 cm) in a temperature-controlled environment (20±2°C), under a 12h light-dark cycle (lights on: 08:00 hours). Food and water are made freely available. Four hours prior to testing, animals are transferred to clean cages and moved to the testing room in order to habituate to the testing environment.

The maze is comprised of a black Perspex annular platform (105cm diameter, 10cm width) elevated to 65cm above ground level, divided equally into four quadrants. Two opposite quadrants are enclosed by clear red Perspex walls (27cm high) on both the inner and outer edges of the platform, while the remaining two opposite quadrants are surrounded only by a Perspex "lip" (1cm high) which serves as a tactile guide to animals on these open areas. To facilitate the measurement of locomotor activity, the apparatus is divided into octants by splitting each quadrant into equal halves using high contrast white lines. The apparatus is illuminated by dim red lighting arranged in such a manner as to provide similar lux levels in both the open and closed quadrants (40-60 lux). A video camera, connected to a VCR in an adjacent observation room, is mounted overhead in order to record behaviour on the maze for subsequent analysis.

Chlordiazepoxide hydrochloride [CDP; Sigma Chemical Co. Ltd,. Poole], which has previously been shown to display robust anxiolytic-like effects in the zero-maze, serves as positive control. Drugs are typically dissolved in a 45% solution of 2-hydroxypropyl-ß-cyclodextrin, and administered orally by gavage 1 hour prior to zero-maze testing.

Rats are placed on a closed quadrant and a 5 min test period is recorded on video-tape. The maze is cleaned with a 5% methanol/water solution and dried thoroughly between test sessions. Five behavioural parameters are scored: [1] percentage of time spent on the open areas; [2] frequency of head dips over the edge of the platform when subjects are located in either the open or the end of the closed quadrants; [3] frequency of stretch-attend postures (SAP) from closed to open quadrants, determined when the subject, on a closed quadrant, exhibits an elongated body posture stretched forward with at least the snout passing over the open/close divide; [4] frequency of rearing; and [5] the number of line crossings. Animals are scored as being in the open area when all four paws were in an open quadrant, and in the closed area only when all four paws passed over the open/closed divide. All testing is carried out between 1100 and 1700 hours.

An increase in the frequency of head dips is considered to be a measure of anxiolytic activity. The compound of example 1 was found to be effective at a dose of 30 mg/Kg.

CHEMISTRY

Preparation of 1-(Diphenylmethyl)-3-azetidinol

This compound was prepared according to the method of Anderson and Lok (*J. Org. Chem.*, **1972**, *37*, 3953, the disclosure of which is incorporated herein by reference), m.p. 111-112 °C (lit. m.p. 113 °C).

Preparation of 3-(4-Chlorobenzyloxy)-1-(diphenylmethyl) azetidine (1)

A solution of 1-diphenylmethyl-3-azetidinol (25 mmol) in DMF (100 mL) was added at 0 °C to a suspension of NaH (60% disp.in oil, 30 mmol) in DMF (50 mL). The reaction mixture was stirred at room temperature for 1h, then 4-chlorobenzylchloride (25 mmol) was added dropwise at 0 °C and the reaction mixture stirred at room temperature for 3 h. The reaction was quenched with water and extracted with ethyl acetate (3 x 50 mL), the extracts were washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography [SiO_2; hexane-ethyl acetate (9:1)] to yield the product as a yellow oil (7.3 g, 80%). The material was used in the next step without further purification.

Example 1. 3-(4-Chlorobenzyloxy)-N-(2-propenyl)azetidine-1-carboxamide (2)

Phosgene solution (1.75-M in toluene, 24 mmol) was added at 0°C to a solution of compound (1) (20 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was stirred at room temperature for 90 min, concentrated *in vacuo*, then redissolved in CH_2Cl_2 (40 mL) and treated with allylamine (42 mmol) at 0°C. The reaction was stirred for 4 h at room temperature, then water (40 mL) was added and the layers were separated. The aqueous layer was extracted with further CH_2Cl_2 (2 x 40 mL). The organic layers were washed with dilute HCl (20 mmol) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated using diethyl ether to give the product (2) as a crystalline solid (3.5 g, 60%), m.p. 110-111 °C. Found: C, 59.84; H, 6.11; N, 9.98. $C_{14}H_{17}ClN_2O_2$ requires: C, 59.89; H, 9.6.10; N, 9.97%.

Preparation of 3-(3,4-Dichlorobenzyloxy)-1-(diphenylmethyl) azetidine (3)

This material was prepared from 1-diphenylmethyl-3-azetidinol (6.0 g) and alpha,3,4-trichlorotoluene using the procedure described for compound (1) (yield 92%).

Example 2. 3-(3,4-Dichlorobenzyloxy)-N-(2-propenyl)azetidine-1-carboxamide (4)

This material was prepared from compound (3) (9.2 g) using the procedure described for compound (2) (yield 75%), m.p. 88-89 °C. Found: C, 53.43; H, 5.18; N, 8.85, $C_{14}H_{16}Cl_2N_2O_2$ requires C, 53.35; H, 5.12; N, 8.88%.

Preparation of 3-(3-(Trifluoromethyl)benzyloxy)-1-(diphenylmethyl)azetidine (5)

This material was prepared from 1-diphenylmethyl-3-azetidinol (5 g) and alpha'-bromo-alpha,alpha,alpha-trifluoro-*m*-xylene using the procedure described for compound (1) (yield 91%).

Example 3. 3-(3-(Trifluoromethyl)benzyloxy)-N-(2-propenyl)azetidine-1-carboxamide (6)

This material was prepared from compound (5) (7.5 g) using the procedure described for compound (1) (yield 64%), m.p. 108°C. Found: C, 57.29; H, 5.44; N, 8.87, $C_{15}H_{17}F_3N_2O_2$ requires C, 57.32; H, 5.45; N, 8.91%.

Preparation of 3-(4-(Trifluoromethyl)benzyloxy)-1-(diphenylmethyl)azetidine (7)

This material was prepared from 1-diphenylmethyl-3-azetidinol (6.0 g) and α'-bromo-α,α,α-trifluoro-*p*-xylene using the procedure described for compound (1) (yield 77%).

Example 4. 3-(4-(Trifluoromethyl)benzyloxy)-N-(2-propenyl)azetidine-1-carboxamide (8)

This material was prepared from compound (7) (7.7 g) using the procedure described for compound (2) (yield 72%), m.p. 120 °C. Found: C, 57.27; H, 5.45; N, 8.86. $C_{15}H_{17}F_3N_2O_2$ requries C, 57.32; H, 5.45, N, 8.91%.

Preparation of 3-(4-Fluorobenzyloxy)-1-(diphenylmethyl) azetidine (9)

This material was prepared from 1-diphenylmethyl-3-azetidinol (6.0 g) and 4-fluorobenzyl bromide using the procedure described for compound (1) (yield 83%).

Example 5. 3-(4-Fluorobenzyloxy)-N-(2-propenyl)azetidine-1-carboxamide (10)

This material was prepared from compound (9) using the procedure described for compound (2), m.p. 97-99 °C. Found: C, 63.57; H, 6.59; N, 10.66. $C_{14}H_{17}ClN_2O_2$ requires C, 63.62; H, 6.48; N, 10.59.

Preparation of 3-(bis-(4-chlorophenyl)methoxy-1-diphenylmethyl)azetidine (11)

A solution of 4,4'-dichlorobenzhydrol (25 mmol), *p*-toluenesulfonic acid (18.4 mmol) and 1-(diphenylmethyl)-3-azetidinol (8.4 mmol) in benzene (100 mL) was heated under reflux in a Dean-Stark apparatus for 3h. The solution was cooled, washed with sodium hydrogen carbonate (saturated aqueous solution, 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography [SiO_2; hexane-diethyl ether (5:1)] to yield the product (11) as a thick oil that crystallized on standing (2.4g, 62%).

Example 6. 3-(Bis(4-chlorophenyl)methoxy)-N-(2-propenyl)azetidine-1-carboxamide (12)

This material was prepared from compound (11) using the procedure described for compound (2) (yield 17%) as a crystalline solid. Found: C, 56.38; H, 5.10; N, 6.51. $C_{20}H_{20}Cl_2N_2O_2.2H_2O$ requires: C, 56.21; H, 5.66; N, 6.56%.

Example 7. Preparation of (*R*)-3-(Bis(4-chlorophenyl)methoxy)-N-(2-hydroxypropyl)azetidine-1-carboxamide (13)

This material was prepared from compound (11) and (*R*)-(-)-1-amino-2-propanol using the procedure described for compound (2) (yield 57%) as a crystalline solid. Found: C, 58.74; H, 5.42; N, 6.84. $C_{20}H_{22}Cl_2N_2O_3$ requires: C, 58.69; H, 5.42; N, 6.84%.

Example 8. 3-(3-Trifluoromethyl)benzyloxy-N-azetidine-1-carboxamide (14)

To a solution of 3-(3-trifluoromethyl)benzyloxy-1-(diphenylmethyl)azetidine (5) (5.3 mmol) in dichloromethane (15 mL) at 0°C, was added a solution of phosgene (1.75M in toluene, 6.4 mmol). The reaction mixture was stirred at room temperature for 2h, concentrated *in vacuo*, then redissolved in THF (15 mL) and treated with ammonium hydroxide (5 mL), added in one portion, at 0°C. The reaction was stirred vigorously for 15h at room temperature, then water (50 mL) and ethyl acetate (40 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated using ethyl acetate (10 mL) to yield (14) as a solid (0.91 g, 63%), mp. 167 °C (ethyl acetate).

Found: C, 52.44; H, 4.72; N, 10.23. $C_{14}H_{17}ClN_2O_2$ requires: C, 52.56; H, 4.78; N, 10.21.

Preparation of 3-(1-(3-trifluoromethylphenyl)ethyloxy)-1-(diphenylmethyl)azetidine (15)

To a solution of α-methyl-3-trifluoromethylbenzyl alcohol (53 mmol), diisopropylethyl amine (105 mmol) in dichloromethane (150 mL) under nitrogen and cooled to 0 °C, was added methane sulfonyl chloride (63.1 mmol) dropwise over 10 min. The reaction was stirred for 15h. Water (200 mL) was added and the resulting mixture stirred for 10min, poured into potassium carbonate (10% wt/wt aqueous solution, 200 mL) and extracted with dichloromethane (3x150 mL). Combined organic extracts were washed with brine (50 mL) once and then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was dissolved in ethyl ether and washed through a pad of silica, eluting with more ether. The filtrate was concentrated *in vacuo*. This material was used directly, as shown below.

A solution of 1-diphenylmethyl-3-azetidinol (42 mmol) in dimethyl formamide (20 mL) was added via pipette, to a suspension of NaH (60% disp.in oil, 50 mmol) in dimethyl formamide (80 mL) at 0°C. The reaction mixture was stirred at room temperature for 15 min, the crude material from above (assumed 53 mmol) was added dropwise as a solution in dimethyl formamide (30 mL) at 0°C and the reaction mixture stirred at room temperature for 2 h. The reaction was poured into water (200 mL) and extracted with ethyl acetate (3 x 50 mL), the extracts were washed with water (200 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2; hexane/ethyl acetate 9/1) to yield 3-(1-(3-trifluoromethylphenyl)ethyloxy)-1-(diphenylmethyl)azetidine (15) as a yellow oil (11.2g, yield 65%). The material was used in the next step without further purification.

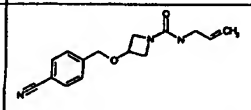
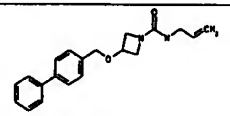
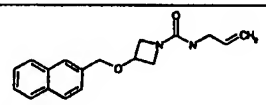
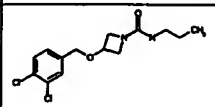
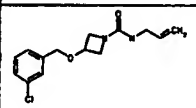
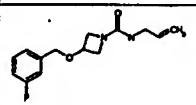
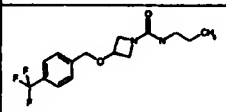
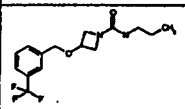
Example 9. 3-(1-(3-Trifluoromethylphenyl)ethyloxy)-azetidine-1-carboxamide (16)

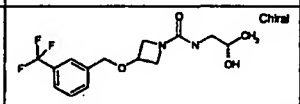
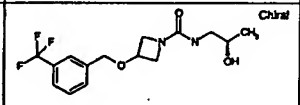
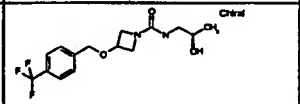
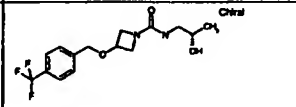
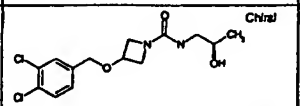
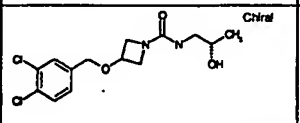
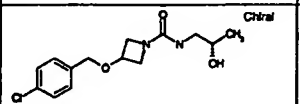
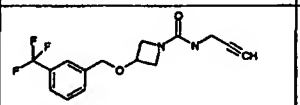
This material was prepared from compound (15) using the procedure described for compound (14) (yield 62%) as a crystalline solid, mp. 130.5-131.5°C (diisopropyl ether). Found: C, 54.24; H, 5.26; N, 9.69. $C_{14}H_{17}ClN_2O_2$requires: C, 54.17; H, 5.24.; N, 9.71.

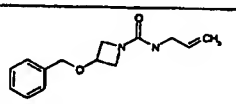
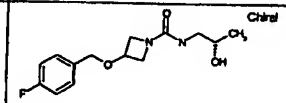
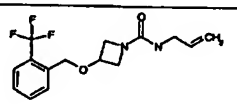
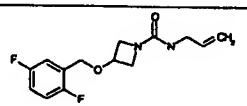
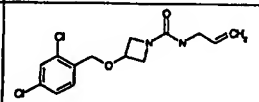
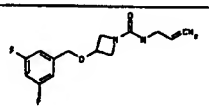
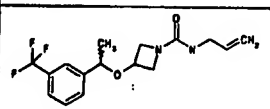
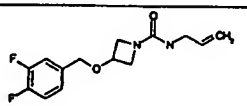
Examples 10 to 43 – see Table 3.

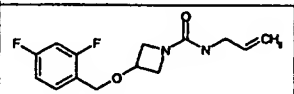
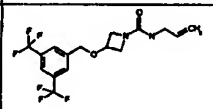
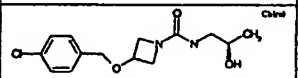
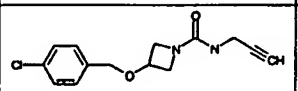
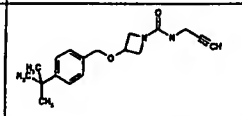
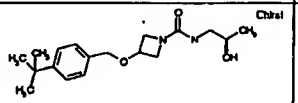
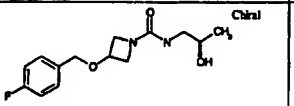
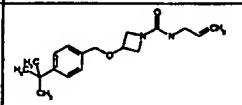
The products were prepared using the procedure described for compound (2).

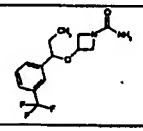
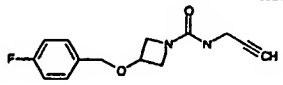
Table 3

Exampleno	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
10	17		C15H17N3O2	271.32	95-96	66.69	6.29	15.32	66.40	6.32	15.48	
11	18		C20H22N2O2	322.41	160.0	74.52	6.87	8.61	74.51	6.88	8.68	
12	19		C18H20N2O2	296.37	141-142	72.96	6.77	9.65	72.95	6.80	9.45	
13	20		C14H18Cl2N2O2	317.22	89-90	53.00	5.74	8.73	53.01	5.72	8.83	
14	21		C14H17ClN2O2	280.76	67-68	59.94	6.12	9.95	59.89	6.10	9.97	
15	22		C14H17FN2O2	264.30	59-60	63.55	6.55	10.59	63.62	6.48	10.59	
16	23		C15H19F3N2O2	316.33	128-129	56.92	6.09	8.83	56.96	6.05	8.85	
17	24		C15H19F3N2O2	316.33	62-63	56.89	6.21	8.82	56.96	6.05	8.85	

Exampleno	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
18	25		C15H19F3N2O3	332.33	67-68	54.25	5.81	8.42	54.21	5.76	8.43	
19	26		C15H19F3N2O3	332.33	67-68	54.21	5.87	8.41	54.21	5.76	8.43	
20	27		C15H19F3N2O3	332.33	97-98	54.09	5.76	8.39	54.21	5.76	8.43	
21	28		C15H19F3N2O3	332.33	97-98	54.39	5.82	8.44	54.21	5.76	8.43	
22	29		C14H18Cl2N2O3	333.22	88-89	50.46	5.34	8.39	50.46	5.44	8.40	
23	30		C14H18Cl2N2O3	333.22	88-89	50.49	5.36	8.61	50.46	5.44	8.40	
24	31		C14H19ClN2O3	298.77	85-86	56.27	6.40	9.35	56.28	6.41	9.37	
25	32		C15H15F3N2O2	312.29	90-91	57.73	4.94	8.91	57.69	4.84	8.97	

Exampleno	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
26	33		C14H18N2O2	246.31	76-77	68.29	7.35	11.37	68.27	7.37	11.37	
27	34		C14H19FN2O3	282.32	73-74	59.49	6.87	9.93	59.56	6.78	9.92	
28	35		C15H17F3N2O2	314.31	63.0	57.34	5.47	8.92	57.32	5.45	8.91	
29	36		C14H16F2N2O2	282.29	75.0	59.59	5.72	9.88	59.57	5.71	9.92	
30	37		C14H16Cl2N2O2	315.20	100.0	53.15	4.99	8.86	53.35	5.12	8.88	
31	38		C14H16F2N2O2	282.29	79.0	59.55	5.73	9.90	59.57	5.71	9.92	
32	39		C16H19F3N2O2	328.34	oil							a
33	40		C14H16F2N2O2	282.29	82.5-85	59.72	5.69	9.98	59.57	5.71	9.92	

Exampleno	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
34	41		C14H16F2N2O2	282.29	91-92.5	59.58	5.62	9.94	59.51	5.71	9.92	
35	42		C16H16F6N2O2	382.31	80.5-81.5	50.38	4.25	7.32	50.27	4.22	7.32	
36	43		C14H19ClN2O3	298.77	76-78	56.94	6.34	10.25	56.28	6.41	9.37	
37	44		C14H15ClN2O2	278.74	123-124	60.88	5.58	9.91	60.33	5.42	10.05	
38	45		C18H24N2O2	300.40	94-96	71.89	8.08	9.28	71.97	8.05	9.32	
39	46		C18H28N2O3	320.44	oil							b
40	47		C14H19FN2O3	282.32	72-73	59.32	6.84	9.81	59.56	6.78	9.92	
41	48		C18H26N2O2	302.42	79-80	71.25	8.79	9.36	71.49	8.67	9.26	

Exampleno	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
42	49		C14H17F3N2O2	302.30	110.5-112	55.64	5.77	9.26	55.63	5.67	9.26	
43	50		C14H15FN2O2	262.29	94-96	64.29	5.47	10.70	64.11	5.76	10.68	

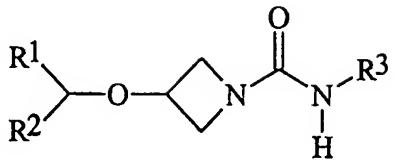
Footnotes for Table 3:

Footnote a: IR: 3296, 2980, 2943, 2877, 1638, 1545, 1400, 1377, 1330, 1203, 1166, 1127, 1073, 706 cm^{-1}.

Footnote b: IR: 3319, 2963, 2872, 1634, 1549, 1469, 1403, 1327, 1269, 1184, 1130, 1083, 818 cm^{-1}.

Claims

1. A compound of formula (1)



(1)

wherein:

R^1 is aryl;

R^2 is H, alkyl or aryl; and

R^3 is hydrogen or alkyl;

and pharmaceutically acceptable addition compounds thereof.

2. A compound according to claim 1 wherein R^1 is a substituted or unsubstituted aryl group selected from phenyl and naphthyl.

3. A compound according to claim 1 or 2 wherein R^1 has 1, 2 or 3 substituent groups.

4. A compound according to claim 1, 2 or 3 wherein R^1 is substituted with one or more substituent groups selected from halo, trifluoromethyl, tertiary-butyl, CN and phenyl.

5. A compound according to claim 4 wherein said halo group is fluoro or chloro.

6. A compound according to any one of claims 1 to 5 wherein R^1 has 1 substituent and is a meta- or para-substituted phenyl group.

7. A compound according to claim 1 wherein R^1 is 3-chlorophenyl, 4-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl or 3,4-difluorophenyl.

8. A compound according to any of claims 1 to 5 wherein R^1 is selected from a 2,4-disubstituted phenyl, a 2,5-disubstituted phenyl, a 3,4-disubstituted phenyl and a 3,5-disubstituted phenyl.

9. A compound according to any of claims 1, 2, 3, 4, 5 or 8 wherein R^1 is substituted by two halo groups, the same or different, or by two trifluoromethyl groups.

10. A compound according to claim 9 wherein R^1 is dichloro or difluoro-substituted.

11. A compound according to any preceding claim wherein R^2 is H.

12. A compound according to any one of claims 1 to 10 wherein R^2 is C_{1-4} alkyl.

13. A compound according to any one of claims 1 to 10 wherein R^2 is mono-substituted phenyl

14. A compound according to any one of claims 1 to 13 wherein R^3 is alkyl.

15. A compound according to any one of claims 1 to 14 wherein R^3 is C_{1-4} alkyl.

16. A compound according to any one of claims 1 to 15 wherein R^3 is alkenyl, alkynyl, hydroxyalkyl or alkoxyalkyl.

17. A compound according to any one of claims 1 to 15 wherein R^3 is unsubstituted saturated cyclic or acyclic hydrocarbyl.

18. A compound according to any one of claims 1 to 15 wherein R^3 is selected from propyl, 2-propenyl, 2-propynyl and 2-hydroxypropyl.

19. A compound according to any one of claims 1 to 13 wherein R^3 is H.

20. A compound according to claim 1 wherein the compound is selected from 3-(4-Chlorobenzyloxy)-N-(2-propenyl) azetidine-1-carboxamide, 3-(3,4-Dichlorobenzyloxy)-N-

(2-propenyl)azetidine-1-carboxamide, 3-(3-(Trifluoromethyl)benzyloxy)-N-(2-propenyl)azetidine-1-carboxamide, 3-(4-(Trifluoromethyl)benzyloxy)-N-(2-propenyl)azetidine-1-carboxamide, 3-(4-Fluorobenzyloxy)-N-(2-propenyl)azetidine-1-carboxamide, 3-(Bis(4-chlorophenyl)methoxy)-N-(2-propenyl)azetidine-1-carboxamide, (R)-3-(Bis(4-chlorophenyl)methoxy)-N-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(1-(3-Trifluoromethylphenyl)ethyloxy)-azetidine-1-carboxamide and 3-(3-(trifluoromethyl)benzyloxy)-azetidine-1-carboxamide.

21. A compound according to any one of claims 1 to 20 for use in therapy.

22. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment (including prophylaxis) of CNS disorders.

23. Use according to claim 22 wherein said medicament is for the treatment (including prophylaxis) of anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness, alcohol withdrawal syndrome, chronic and acute pain, neurodegenerative diseases, symptoms relating to withdrawal from substance abuse or spasticity.

24. Use according to claim 22 wherein said medicament is for the treatment (including prophylaxis) of anxiety or epilepsy.

25. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for muscle relaxation prior to surgery or surgical manipulation or as pre-medication prior to surgery.

26. A pharmaceutical composition comprising a compound according to any one of claims 1 to 20 in combination with a pharmaceutically acceptable carrier or excipient.

27. A method of treatment (including prophylaxis) of CNS disorders comprising administering to a patient in need of such treatment an effective dose of a compound according to any one of claims 1 to 20.

28. A method according to claim 27 wherein said method is for the treatment of anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness, alcohol withdrawal syndrome, chronic and acute pain, neurodegenerative diseases, symptoms relating to withdrawal from substance abuse or spasticity.

29. A method according to claim 27 wherein said method is for the treatment of anxiety or epilepsy.

30. A method of muscle relaxation prior to surgery or surgical manipulation or a method of pre-medication prior to surgery, comprising administering to a patient in need thereof an effective dose of a compound according to any one of claims 1 to 20.

INTERNATIONAL SEARCH REPORT

Interi nal Application No
PCT/GB 99/00219

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D205/04 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 872 447 A (LEPETIT S.P.A.) 12 July 1961 see the whole document	1,21,26
A	EP 0 102 194 A (ROBINS CO INC A H) 7 March 1984 see claims	1-30
A	EP 0 194 112 A (ROBINS CO INC A H) 10 September 1986 cited in the application see claims	1-30

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 April 1999	07/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/00219

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 27-30
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 27-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr ial Application No
PCT/GB 99/00219

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